The Fetal Brain: Sensitive to a Mother’s Own Childhood Environment?

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First Annual UK Maternal Mental Health Alliance Conference, London, UK
September 13th, 2017
Childhood Trauma: Physiological and Psychological Sequelae

Early life experiences ➞ long-term effects

- History of childhood trauma:
  - ↑ psychological disorders (depression, anxiety disorders, antisocial behavior, PTSD, substance abuse)
    (Anda 2006; Briere & Elliott, 2003; MacMillan, 2001; Schilling, 2007; Widom, 1999)
  - altered HPA axis reactivity
    (Bremner, 2003; Elzinga, 2008; Heim, 2000, 2008; Carpenter, 2011; Tyrka, 2009)
  - ↑ inflammatory milieu
    (Danese, 2007, 2008; Dube 2009; Rooks, 2012; Slopen, 2013)
  - ↑ obesity
    (Alvarez, 2007; Greenfield & Marks, 2009; Rhode, 2008; Springer 2007; Thomas 2008)
Intergenerational Transmission of the Effects of Maternal Childhood Trauma

Children whose mothers experienced abuse/neglect in their childhood:

- ↑ disruptive behavior disorder/ conduct problems
  (Collishaw et al., 2007; Miranda et al., 2011)

- ↑ internalizing and externalizing problems
  (Dubowitz et al., 2001; Rijlaarsdam et al. 2014; Thompson et al., 2007)

- ↑ likelihood for autism spectrum disorders (ASD)
  (Roberts et al., 2013)

- ↑ adverse birth outcomes, obesity
  (Roberts et al. 2014; Smith et al. 2016)
Intergenerational Transmission of the Effects of Maternal Childhood Trauma

Maternal Life Span

Childhood Trauma

Pregnancy

• ↑ Psychopathology
• Altered endocrine and immune/inflammatory stress biology

Motherhood

Offspring Life Span

Prenatal
• Altered maternal-placental-fetal stress biology

↑ Psychopathology

Postnatal
• Maternal depression
• ↓ Maternal sensitivity

Offspring Brain Development
Intergenerational Transmission of the Effects of Maternal Childhood Trauma

CT-associated alterations in offspring physiology present at birth?

1) Are alterations in brain anatomy in offspring of mothers with childhood trauma exposure evident at birth (no postnatal influences yet)?
2) Do these neuroanatomical alterations account for behavioral difficulties in infants of mothers exposed to childhood trauma?
Methods

N=80 Mother-fetal/infant dyads
Prospective longitudinal study from early pregnancy to infancy

Maternal childhood trauma
• Childhood Trauma Questionnaire (CT+ group: at least 1 type of trauma/neglect above the moderate/severe cut-off)

Newborn brain anatomy
• MRI-based assessment of total and regional tissue volume based on T1- and T2 weighted images applying an atlas-moderated iterative expectation maximization segmentation algorithm
  (Gilmore et al. 2007, Avants et al. 2011)

Infant social-emotional development
• Social-Emotional Scale of the Bayley Scales of Infant Development – Third Edition

Covariates included in the analyses
• Gestational age at birth, postnatal age at MRI scan, maternal socioeconomic status, obstetric complications, maternal depression during pregnancy, infant sex
• Additionally for social-emotional development: maternal postnatal depression, maternal sensitivity
## Descriptives

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Complete sample N = 80</th>
<th>CT- group (no childhood trauma) n = 52 (65%)</th>
<th>CT+ group (≥ 1 type of childhood trauma) n = 28 (35%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age at baseline, yrs, mean ± SD</td>
<td>28.06 ± 5.5</td>
<td>28.54 ± 5.7</td>
<td>27.18 ± 5.2</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Non-Hispanic White, n(%)</td>
<td>31 (39.7%)</td>
<td>26 (51%)</td>
<td>5 (18.5%)</td>
</tr>
<tr>
<td>Hispanic White, n(%)</td>
<td>26 (33.3%)</td>
<td>15 (29.4%)</td>
<td>11 (40.7%)</td>
</tr>
<tr>
<td>Presence of any obstetric risk condition, n (%)</td>
<td>20 (25%)</td>
<td>14 (26.9%)</td>
<td>6 (21.4%)</td>
</tr>
<tr>
<td>Depression in pregnancy (CES-D), mean ± SD</td>
<td>15.07 ± 8.9</td>
<td>13.6 ± 8.3</td>
<td>17.80 ± 9.3*</td>
</tr>
<tr>
<td>Female infant sex, n (%)</td>
<td>32 (40%)</td>
<td>23 (42.3%)</td>
<td>10 (35.7%)</td>
</tr>
<tr>
<td>Gestational age at birth, wks, mean ± SD</td>
<td>39.11 ± 1.5</td>
<td>39.04 ± 1.4</td>
<td>39.24 ± 1.6</td>
</tr>
<tr>
<td>Age at MRI scan, days, mean ± SD</td>
<td>26.0 ± 13.1</td>
<td>24.77 ± 12.3</td>
<td>28.29 ± 14.6</td>
</tr>
</tbody>
</table>
Maternal Childhood Trauma and Newborn Brain Anatomy

GMV: $F_{1,72} = 9.32, p = .003^*$
WMV: $F_{1,72} = 4.23, p = .043$
CSF: $F_{1,72} = 1.27, p = .264$
ICV: $F_{1,72} = 7.05, p = .010^*$

*Bonferroni corrected $\alpha=0.0125$

Moog, …, Buss 2017, Biol. Psychiatry
Maternal Childhood Trauma and Newborn Brain Anatomy

Global, not regionally specific, effects of maternal childhood trauma.

Moog, ..., Buss 2017, Biol. Psychiatry
Maternal Childhood Trauma, Newborn Brain Anatomy and Infant Social-emotional Development

Maternal Childhood Trauma

Newborn Gray Matter Volume (cm³)

Infant Social-Emotional Development

Indirect effect: -.83, BC CI [-2.11, -.18]

→ Maternal childhood trauma-associated reduction in newborn gray matter volume mediates the association between maternal childhood trauma and delayed social-emotional development at 6-mo age.
Summary

• Maternal exposure to CT is associated with a reduction in overall brain volume in their newborn children.
• The main contributor to this effect is a significant global reduction of cortical gray matter.
• Mediated by gray matter volume, maternal CT has a negative effect on infant social-emotional development.

➔ The intergenerational transmission of CT effects may begin as early as during the child’s intrauterine period of life.

➔ What kind of signals may the fetus receive about maternal childhood experiences?
Intergenerational Transmission of the Effects of Maternal Childhood Trauma – Framework

CHILDHOOD TRAUMA

Psychological depression, PTSD
Biological endocrine, immune
Biophysical obesity
Behavioral smoking, drug use sexual behavior

Maternal Psychological state
Maternal Parenting Behavior

PREGNANCY

Maternal compartment
Fetal compartment

Biophysical obesity
Behavioral smoking, drug use sexual behavior

Maternal BIOLOGICAL STATE
endocrine immune oxytocinergic

Trauma in adult life

gern line epigenetic transmission(?)

INFANCY

Buss et al. 2017, JAACAP
Maternal Childhood Trauma and Gestational Stress Biology

Maternal childhood trauma is associated with altered gestational stress biology

- ↑ cortisol awakening response
  (Bublitz et al. 2012, 2013, 2014)

- ↑ hair cortisol concentration
  (Schreier et al. 2015)

- ↑ placental corticotrophin-releasing hormone (CRH) concentration
  (Moog et al. 2015)

- ↑ thyroid stimulating hormone (TSH) concentration
  (Moog et al. 2017)
Maternal Childhood Trauma and Placental CRH during Pregnancy

N=295

CT*GA: $B(SE) = 0.005 (0.002)$, $t_{415}=2.322$, $p=.02$

Adjusted for race/ethnicity, childhood SES, parity, income, pre-pregnancy BMI, obstetric risk, smoking, drugs, alcohol, and depression

Moog, Buss et al. 2015, Biological Psychiatry
Maternal Childhood Trauma and Thyroid Function during Pregnancy

![Graph showing TSH levels during pregnancy](image)

*Moog, …, Buss, 2017, PNEC*
Maternal Childhood Trauma and Cortisol Concentrations during Pregnancy

Bublitz et al. 2012: *Maternal CT* (sexual abuse) *is associated with a higher cortisol awakening response in the 2\textsuperscript{nd} and 3\textsuperscript{rd} trimesters of pregnancy.*
Maternal Childhood Trauma and Interleukin-6 Concentrations during Pregnancy

![Graph showing the comparison of Mean IL-6 (pg/mL) between 'No' and 'Yes' categories.](image)

UCI (N=144)

CTQ Sexual Abuse (severe cut-off)

P<0.05
Stress signals as “programming cues”

Mother

Placenta

Fetus

Brain Development
- Proliferation, Migration
- Differentiation
- Neurogenesis
- Growth of axons and dendrites
- Synapse formation
- Apoptosis / Pruning
- Myelination

Endocrine: **Cortisol**, **CRH**, **TSH**

Immune: CRP, **IL-6**, **TNF-a**

- Transcription factors
- Neurotrophic factors
- Neurotransmitters
- Growth hormones
- Thyroid hormones

**Early Environment**

- (Early Life) Stress
  - Obesity
  - Undernutrition
  - Obstetric complications (e.g. infection)

Maternal and Fetal Genotype

**Cognitive and Affective Processes**
- Mental Health

Buss et al. 2012, Science Signaling
Maternal cortisol over the course of pregnancy and subsequent child amygdala and hippocampus volumes and affective problems

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Edited by Bruce S. McEwen, The Rockefeller University, New York, NY, and approved March 19, 2012 (received for review January 24, 2012)

Figure 1

A) Girls

B) Boys

C) 

Small right amygdala volume (lowest tertile) in the child

Large right amygdala volume (highest tertile) in the child
Maternal Cortisol Concentrations during Pregnancy and Newborn Amygdala Volume

N=88

* Controlled for gestational age at sample collection, obstetric complications, smoking, drug use, parental psychiatric illness, gestational age at birth and age at MRI scan
Mean Gestational IL-6 and Newborn Amygdala Volume

Graham, …, Buss, 2017, Biol Psychiatry
Larger Neonatal Right Amygdala Volume and Lower Impulse Control at 24-months-age

\[ \beta = -0.311, \quad p = 0.021 \]

Adjusting for

- Infant sex
- Gestational age at birth
- Postnatal environment, attachment
Mean Gestational IL-6 and Newborn Amygdala Connectivity

Graham, …, Buss, 2017, Biol Psychiatry
Mean Gestational IL-6 and Newborn Uncinate Fasciculus Maturity
Summary

• Maternal exposure to CT is associated with specific changes in maternal-placental-fetal stress biology.
• The same changes in maternal-placental-fetal stress biology have the potential to alter fetal brain development.
  – The amygdala is a particularly sensitive target.
Prenatal Origins of Postnatal Behavior?

Toepfer, …, Buss, 2017, Neurosci & Biobehav Reviews
Maternal Oxytocinergic Adaptations during Pregnancy and Maternal Parenting Behavior

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Parameter Estimates</th>
<th>t-value</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.689</td>
<td>11.975</td>
<td>2e-16 ***</td>
</tr>
<tr>
<td>Intrusiveness</td>
<td>0.007</td>
<td>0.883</td>
<td>0.379</td>
</tr>
<tr>
<td>Time</td>
<td>-0.026</td>
<td>-3.372</td>
<td>0.000947 ***</td>
</tr>
<tr>
<td>Age</td>
<td>-0.003</td>
<td>-1.542</td>
<td>0.126330</td>
</tr>
<tr>
<td>PC1</td>
<td>-0.101</td>
<td>-0.954</td>
<td>0.3425</td>
</tr>
<tr>
<td>PC2</td>
<td>0.008</td>
<td>0.080</td>
<td>0.9368</td>
</tr>
<tr>
<td>PC3</td>
<td>0.061</td>
<td>1.122</td>
<td>0.5414</td>
</tr>
<tr>
<td>SES</td>
<td>0.01</td>
<td>0.613</td>
<td>0.3644</td>
</tr>
<tr>
<td>Time*Intrusiveness</td>
<td>0.006</td>
<td>2.001</td>
<td>0.0472 *</td>
</tr>
</tbody>
</table>

DNA methylation of OXT cg16887334 during pregnancy

DNA methylation of OXT cg16887334 during pregnancy and maternal intrusiveness
Conclusion

- Maternal CT-associated alteration of **newborn** brain anatomy and its implication for infant social-emotional behavior suggest **intrauterine transmission pathways**.
- CT-associated alteration in maternal-placental-fetal stress biology, that may alter fetal neurodevelopmental trajectories as well as maternal parenting behavior, is a likely biological transmission pathway.
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Oregon Health & Science University
Damien Fair
Alice Graham

MPI München
Elisabeth Binder
Nadine Provencal

University of Helsinki
Katri Räikkönen

Funding
ERA-Net Neuron
European Research Council
National Institutes of Health (NIH)